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Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency

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We report the updated classification of primary immunodeficiency diseases, compiled by the *ad hoc* Expert Committee of the International Union of Immunological Societies. As compared to the previous edition, more than 15 novel disease entities have been added in the updated version. For each disorders, the key clinical and laboratory features are provided. This updated classification is meant to help in the diagnostic approach to patients with these diseases.

Keywords: primary immunodeficiency diseases

The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency met in New York City, May 31–June 1, 2011 to update the classification of human primary immunodeficiencies (PIDs). Novel developments in gene discovery and increased knowledge in the mechanisms that govern immune system development and function have resulted in the identification of several novel PIDs in the last 2 years.

The classification of primary immunodeficiencies (PIDs) provides a framework to help in the diagnostic approach to patients. As in recent classifications, eight major groups of PIDs have been included in the Tables; however the order of the Tables has been changed with **Table 2** now describing the "Well-defined syndromes with immunodeficiency" (previously **Table 3**) to reflect the immunological similarity between the disorders included in this Table and those in **Table 1**, "Combined immunodeficiencies."

Any classification of human disorders is somewhat arbitrary, and the classification of PIDs is no exception. Some disorders might well belong to more than one group. CD40 ligand deficiency, for example, is reported both in **Tables 1** and **3** ("Predominantly antibody deficiencies"), to reflect the facts that failed B cell isotype switching was historically the most prominent feature of this condition (originally named Hyper-IgM syndrome) and that some patients survive into adulthood without significant opportunistic infections and do well with only immunoglobulin replacement therapy. Explanatory notes provided after each Table offer additional information (particularly where a condition appears in more than one Table) and indicate which new disorders have been added to that Table.

Although this updated classification reports on the most typical immunological findings and associated clinical and genetic features for the various PIDs, there is extensive clinical, immunological, and molecular heterogeneity that can not be easily recapitulated in a brief summary. To facilitate a more rigorous analysis of each disease, a column has been added on the right with a hyperlink to refer to its catalog number in the Online Mendelian Inheritance in Man (OMIM) publicly accessible database (www.omim.org) of human genetic disorders. It is suggested that the reader consult this regularly updated and fully referenced resource.

The prevalence of the various PIDs varies in different countries. For this reason, in this new classification, we have elected to avoid giving a comment on the relative frequency of PID disorders. However, an asterisk has been placed in the first column, after the disease name, to identify disorders for which fewer than 10 unrelated cases have been reported in the literature. Some of these forms of PID can be considered extremely rare. Others have only recently been identified and it may be that more patients will be detected over time.

Finally, it is increasingly recognized that different mutations in the same gene may result in different phenotypes and may be associated with different patterns of inheritance. This concept of clinical, immunological, and genetic heterogeneity is assuming foremost importance. Notes in the text or in the footnotes identify such heterogeneity, when known.

The scope of the IUIS Expert Committee on Primary Immunodeficiency is to increase awareness, facilitate recognition, and promote optimal treatment for patients with Primary Immunodeficiency disorders worldwide. For this reason, in addition to periodically revising the Classification of PIDs, the Expert Committee is also actively involved in the development of diagnostic criteria and in providing, upon request, advice with regard to therapeutic guidelines.

Table 1 | Combined immunodeficiencies.

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheri-tance	Genetic defect/ presumed pathogenesis	OMIM number
1. T^-B^+ Severe combined immunodeficiency (SCID)							
(a) γc deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells; leaky cases may present with low to normal T and/or NK cells or Omenn syndrome	XL	Defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21	300400
(b) JAK3 deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells; leaky cases may present with variable T and/or NK cells	AR	Defect in Janus activating kinase 3	600173
(c) IL7Rα deficiency	Markedly decreased	Normal or increased	Decreased	Normal NK cells	AR	Defect in IL-7 receptor α chain	146661
(d) CD45 deficiency*	Markedly decreased	Normal	Decreased	Normal γ/δ T cells	AR	Defect in CD45	151460
(e) CD3δ*/ CD3ε*/CD3ζ* deficiency	Markedly decreased	Normal	Decreased	Normal NK cells No γ/δT cells	AR	Defect in CD3δ, CD3ε, or CD3ζ chains of T cell antigen receptor complex	186790, 186830, 186740
(f) Coronin-1A deficiency*	Markedly decreased	Normal	Decreased	Detectable thymus	AR	Defective thymic egress of T cells and defective T cell locomotion	605000
2. T^-B^- SCID							
(a) RAG 1/2 deficiency	Markedly decreased	Markedly decreased	Decreased	May present with Omenn syndrome, expanded γ/δT cells, autoimmunity, and/or granulomas	AR	Defective VDJ recombination; defect of recombinase activating gene (RAG) 1 or 2	601457
(b) *DCLRE1C* (Artemis) deficiency	Markedly decreased	Markedly decreased	Decreased	Defective VDJ recombination, radiation sensitivity; may present with Omenn syndrome	AR	Defective VDJ recombination; defect in Artemis DNA recombinase repair protein	602450
(c) DNA-PKcs deficiency*	Markedly decreased	Markedly decreased	Decreased	(Widely studied *scid* mouse defect)	AR	Defective VDJ recombination; defect in DNA-PKcs recombinase repair protein	600899
(d) Reticular dysgenesis, AK2 deficiency	Markedly decreased	Decreased or normal	Decreased	Deficiency of T, B, and NK cells with granulocytopenia, deafness	AR	Defective maturation of lymphoid and myeloid cells (stem cell defect) defect in mitochondrial adenylate kinase 2	103020
(e) Adenosine deaminase (ADA) deficiency	Absent from birth (null mutations) or progressive decrease	Absent from birth of progressive decrease	Progressive decrease	Decreased NK cells, often with costochondral junction flaring, neurological features, hearing impairment, lung, and liver manifestations; partial ADA deficiency may lead to delayed or milder presentation	AR	Absent ADA activity, elevated lymphotoxic metabolites (dATP, *S*-adenosylhomocysteine)	102700

(Continued)

Table 1 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
3. Omenn syndrome	Present; restricted heterogeneity	Normal or decreased	Decreased, except increased IgE	Erythroderma, eosinophilia, adenopathies, hepatosplenomegaly	AR	Hypomorphic mutations in RAG1/2, Artemis, IL7Rα, RMRP, ADA, DNA Ligase IV, γc, or associated with DiGeorge syndrome; some cases have no defined gene mutation	603554
4. DNA ligase IV deficiency	Decreased	Decreased	Decreased	Microcephaly, facial dysmorphisms, radiation sensitivity; may present with Omenn syndrome or with a delayed clinical onset	AR	DNA ligase IV defect, impaired non-homologous end joining (NHEJ)	601837
5. Cernunnos/ *NHEJ1* deficiency*	Decreased	Decreased	Decreased	Microcephaly, *in utero* growth retardation, radiation sensitivity	AR	Cernunnos (*NHEJ1*) defect, impaired non-homologous end joining	611291
6. CD40 ligand deficiency	Normal; may progressively decrease	IgM^+ and IgD^+ B cells present, other isotypes absent	IgM increased or normal, other isotypes decreased	Neutropenia, thrombocytopenia; hemolytic anemia, biliary tract, and liver disease, opportunistic infections	XL	Defects in CD40 ligand (CD40L) cause defective isotype switching and impaired dendritic cell signaling	300386
7. CD40 deficiency*	Normal	IgM^+ and IgD^+ B cells present, other isotypes absent	IgM increased or normal, other isotypes decreased	Neutropenia, gastrointestinal, and liver/biliary tract disease, opportunistic infections	AR	Defects in CD40 cause defective isotype switching and impaired dendritic cell signaling	109535
8. Purine nucleoside phosphorylase (PNP) deficiency	Progressive decrease	Normal	Normal or decreased	Autoimmune hemolytic anemia, neurological impairment	AR	Absent PNP, T cell and neurologic defects from elevated toxic metabolites, especially dGTP	164050
9. CD3γ deficiency*	Normal, but reduced TCR expression	Normal	Normal		AR	Defect in CD3 γ	186740
10. CD8 deficiency*	Absent CD8, normal CD4 cells	Normal	Normal		AR	Defects of CD8 α chain	186910
11. ZAP-70 deficiency	Decreased CD8, normal CD4 cells	Normal	Normal		AR	Defects in ZAP-70 signaling kinase	176947
12. Ca^{++} channel deficiency							
(a) ORAI-I deficiency*	Normal number, but defective TCR-mediated activation	Normal	Normal	Autoimmunity, anhydrotic ectodermic dysplasia, non-progressive myopathy	AR	Defect in ORAI-1, a Ca^{++} release-activated channel (CRAC) modulatory component	610277

(Continued)

Table 1 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheri-tance	Genetic defect/ presumed pathogenesis	OMIM number
(b) STIM-1 deficiency*	Normal number, but defective TCR-mediated activation	Normal	Normal	Autoimmunity, anhydrotic ectodermic dysplasia, non-progressive myopathy	AR	Defect in STIM-1, a stromal interaction molecule Ca^{++}sensor	605921
13. MHC class I deficiency	Decreased CD8, normal CD4	Normal	Normal	Vasculitis	AR	Mutations in *TAP*1, *TAP*2 or *TAPBP* (tapasin) genes giving MHC class I deficiency	604571
14. MHC class II deficiency	Normal number, decreased CD4 cells	Normal	Normal or decreased	Failure to thrive, diarrhea, respiratory tract infections	AR	Mutation in transcription factors for MHC class II proteins (*CIITA*, *RFX*5, *RFXAP*, *RFXANK* genes)	209920
15. Winged helix deficiency (nude)*	Markedly decreased	Normal	Decreased	Alopecia, abnormal thymic epithelium, impaired T cell maturation (widely studied nude mouse defect)	AR	Defects in forkhead box N1 transcription factor encoded by *FOXN*1, the gene mutated in nude mice	600838
16. Complete DiGeorge syndrome	Profoundly decreased	Low to normal	Decreased	Lymphoproliferation (lymphadenopathy, hepatosplenomegaly), autoimmunity (may resemble IPEX syndrome), impaired T cell proliferation	AD	Deletion of chromosome 22q11.2 or in a minority of cases other chromosomal regions, including 10p; heterozygous defects in transcription factor *TBX1*	188400
17. Cartilage hair hypoplasia	Decreased or normal; impaired lymphocyte proliferation	Normal	Normal or reduced. Antibodies variably decreased	Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine	AR	Mutations in *RMRP* (RNase MRP RNA) Involved in processing of ribosomal RNA, mitochondrial DNA replication and cell cycle control	250250
18. IKAROS deficiency*	Normal, but impaired lymphocyte proliferation	Absent	Presumably decreased	Anemia, neutropenia, thrombocytopenia	AD *de novo*	Mutation in *IKAROS*, a hematopoietic specific zinc-finger protein and a central regulator of lymphoid differentiation	
19. STAT5b deficiency*	Modestly decreased	Normal	Normal	Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity	AR	Defects of STAT5b, impaired development and function of γδT cells, Treg, and NK cells, impaired T cell proliferation	604260
20. ITK deficiency*	Modestly decreased	Normal	Normal or decreased		AR	Defects in *ITK*, EBV associated lymphoproliferation	613011
21. MAGT1 deficiency*	Decreased CD4 cells	Normal	Normal	EBV infection, lymphoma; viral infections, respiratory and GI infections	XL	Mutations in *MAGT1*, impaired Mg^{++} flux leading to impaired TCR signaling	300715

(Continued)

Table 1 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheri-tance	Genetic defect/ presumed pathogenesis	OMIM number
22. DOCK8 deficiency	Decreased	Decreased	Low IgM, increased IgE	Low NK cells, hypereosinophilia, recurrent infections; severe atopy, extensive cutaneous viral, and bacterial (staph.) infections, susceptibility to cancer	AR	Defect in *DOCK*8	243700

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; SCID, severe combined immune deficiency; EBV, Epstein Barr virus; Ca^{++}, calcium; MHC, major histocompatibility complex.
**Ten or fewer unrelated cases reported in the literature.*

*Three disorders have been added to **Table 1**: DOCK8 deficiency, IKAROS deficiency, and MAGT1 deficiency.*

*Infants with SCID who have maternal T cells engraftment may have T cells that do not function normally; these cells may cause autoimmune cytopenias or graft versus host disease. Hypomorphic mutations in several of the genes that cause SCID may result in Omenn syndrome (OS), or "leaky" SCID. Both of these disorders can be associated with higher numbers of T cells and reduced rather than absent activation responses when compared with typical SCID caused by null mutations. A spectrum of clinical findings including typical SCID, OS, leaky SCID, and granulomas with T lymphopenia can be found in patients with RAG gene defects. RAC2 deficiency is a disorder of leukocyte motility and is reported in **Table 5**; however, one patient with RAC2 deficiency was found to have absent T cell receptor excision circles (TRECs) by newborn screening, but T cell numbers and mitogen responses were not impaired. For additional syndromic conditions with T cell lymphopenia, such as DNA repair defects, cartilage hair hypoplasia, IKAROS deficiency, and NEMO syndrome, see **Tables 2** and **6**; however, it should be noted that individuals with the most severe manifestations of these disorders could have clinical signs and symptoms of SCID. Severe folate deficiency (such as with malabsorption due to defects in folate carrier or transporter genes SLC10A1 or PCFT) and some metabolic disorders, such as methylmalonicaciduria, may present with reversible profound lymphopenia in addition to their characteristic presenting features.*

Table 2 | Well-defined syndromes with immunodeficiency.

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
1. Wiskott–Aldrich syndrome (WAS)	Progressive decrease, abnormal lymphocyte responses to anti-CD3	Normal	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE	Thrombocytopenia with small platelets; eczema; lymphoma; autoimmune disease; IgA nephropathy; bacterial and viral infections. XL thrombocytopenia is a mild form of WAS, and XL neutropenia is caused by missense mutations in the GTPase binding domain of WASP	XL	Mutations in *WAS*; cytoskeletal and immunologic synapse defect affecting hematopoietic stem cell derivatives	301000
2. DNA repair defects (other than those in Table 1)							
(a) Ataxia–telangiectasia	Progressive decrease	Normal	Often decreased IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased	Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased alpha fetoprotein and X-ray sensitivity; chromosomal instability	AR	Mutations in *ATM*; disorder of cell cycle checkpoint and DNA double strand break repair	208900
(b) Ataxia–telangiectasia-like disease (ATLD)*	Progressive decrease	Normal	Antibodies variably decreased	Moderate ataxia; pulmonary infections; severely increased radiosensitivity	AR	Hypomorphic mutations in *MRE*11; disorder of cell cycle checkpoint and DNA double-strand break repair	604391
(c) Nijmegen breakage syndrome	Progressive decrease	Variably reduced	Often decreased IgA, IgE, and IgG subclasses; increased IgM; antibodies variably decreased	Microcephaly; bird like face; lymphomas; solid tumors; ionizing radiation sensitivity; chromosomal instability	AR	Hypomorphic mutations in *NBS*1 (*Nibrin*); disorder of cell cycle checkpoint and DNA double-strand break repair	251260
(d) Bloom syndrome	Normal	Normal	Reduced	Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability	AR	Mutations in *BLM*; RecQ like helicase	210900
(e) Immunodeficiency with centromeric instability and facial anomalies (ICF)	Decreased or normal; Responses to PHA may be decreased	Decreased or normal	Hypogammaglobulinemia; variable antibody deficiency	Facial dysmorphic features; macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multiradial configurations of chromosomes 1, 9, 16; no DNA breaks	AR	Mutations in DNA methyltransferase *DNMT3B* (ICF1) resulting in defective DNA methylation; or in *ZBTB*24 (ICF2)	242860

(Continued)

Table 2 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
(f) PMS2 deficiency (class switch recombination deficiency due to impaired mismatch repair)	Normal	Switched and non-switched B cells are reduced	Low IgG and IgA, elevated IgM, abnormal antibody responses	Recurrent infections; café-au-lait spots; lymphoma, colorectal carcinoma, brain tumor	AR	Mutations in *PMS2*, resulting in defective CSR-induced DNA double-strand breaks in Ig switch regions	600259
(g) Riddle syndrome*	Normal	Normal	Low IgG	Mild motor control and learning difficulties, mild facial dysmorphism, and short stature	AR	Mutations in *RNF168*, resulting in defective DNA double-strand break repair	611943
3. Thymic defects							
DiGeorge anomaly (chromosome 22q11.2 deletion syndrome)	Decreased or normal	Normal	Normal or decreased	Hypoparathyroidism, conotruncal malformation; abnormal facies; large deletion (3 Mb) in 22q11.2 (or rarely a deletion in 10p)	*De novo* defect or AD	Contiguous gene defect in 90% affecting thymic development; mutation in *TBX1*	188400
4. Immune-osseous dysplasias							
(a) Cartilage hair hypoplasia	Decreased or normal; impaired lymphocyte proliferation	Normal	Normal or reduced. Antibodies variably decreased	Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine	AR	Mutations in *RMRP* (RNase MRP RNA) Involved in processing of ribosomal RNA, mitochondrial DNA replication and cell cycle control	250250
(b) Schimke syndrome	Decreased	Normal	Normal	Short stature, spondyloepiphyseal dysplasia, intrauterine growth retardation, nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure	AR	Mutations in *SMARCAL1*, involved in chromatin remodeling	242900
5. Comel–Netherton syndrome	Normal	Switched and non-switched B cells are reduced	Elevated IgE and IgA antibody variably decreased	Congenital ichthyosis, bamboo hair, atopic diathesis, increased bacterial infections, failure to thrive	AR	Mutations in *SPINK5* resulting in lack of the serine protease inhibitor LEKTI, expressed in epithelial cells	256500
6. Hyper-IgE syndromes (HIES)							
(a) AD-HIES (Job syndrome)	Normal Th-17 cells decreased	Normal (switched and non-switched memory B cells are reduced; BAFF level increased)	Elevated IgE; specific antibody production decreased	Distinctive facial features (broad nasal bridge), eczema, osteoporosis, and fractures, scoliosis, failure/delay of shedding primary teeth, hyperextensible joints, bacterial infections (skin and pulmonary abscesses, pneumatoceles) due to *Staphylococcus aureus*, candidiasis	AD, often *de novo* defect	Dominant-negative heterozygous mutations in *STAT3*	

(Continued)

Table 2 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
(b) AR-HIES				No skeletal and connective tissue abnormalities; no pneumatoceles	AR		
(i) TYK2 deficiency*	Normal, but multiple cytokine signaling defect	Normal	(±) Elevated IgE	Susceptibility to intracellular bacteria (mycobacteria, *Salmonella*), fungi, and viruses		Mutation in *TYK*2	611521
(ii) DOCK8 deficiency	Reduced	Reduced	(±) Elevated IgE, low IgM	Recurrent respiratory infections; extensive cutaneous viral and staphylococcal infections, increased risk of cancer, severe atopy with anaphylaxis		Mutation in *DOCK*8	611432
(iii) Unknown origin	Normal	Normal	Elevated IgE	CNS hemorrhage, fungal, and viral infections		Unknown	
7. Hepatic veno-occlusive disease with immunodeficiency (VODI)	Normal (decreased memory T cells)	Normal (decreased memory B cells)	Decreased IgG, IgA, IgM absent germinal centers absent tissue plasma cells	Hepatic veno-occlusive disease; *Pneumocystis jiroveci* pneumonia; susceptibility to CMV, candida; thrombocytopenia; hepatosplenomegaly	AR	Mutations in *SP*110	235550
8. Dyskeratosis congenita (DKC)							
(a) XL-DKC (Hoyeraal-Hreidarsson syndrome)	Progressive decrease	Progressive decrease	Variable	Intrauterine growth retardation, microcephaly, nail dystrophy, recurrent infections, digestive tract involvement, pancytopenia, reduced number and function of NK cells	XL	Mutations in dyskerin (*DKC*1)	305000
(b) AR-DKC*	Abnormal	Variable	Variable	Pancytopenia, sparse scalp hair and eyelashes, prominent periorbital telangiectasia, and hypoplastic/dysplastic nails	AR	Mutation in *NOLA2* (*NHP*2) or in *NOLA3* (*NOP10*)	224230
(c) AD-DKC	Variable	Variable	Variable	Reticular hyperpigmentation of the skin, dystrophic nails, osteoporosis, premalignant leukokeratosis of the mouth mucosa, palmar hyperkeratosis, anemia, pancytopenia	AD	Mutation in *TERC* Mutation in *TERT* Mutation in *TINF*2	127550

(Continued)

Table 2 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
9. IKAROS deficiency*	Normal, but impaired lymphocyte proliferation	Absent	Presumably decreased	Anemia, neutropenia, thrombocytopenia	AD *de novo*	Mutation in *IKAROS*, a hematopoietic specific zinc-finger protein and a central regulator of lymphoid differentiation	

SCID, severe combined immune deficiency; XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; MSMD, Mendelian susceptibility of mycobacterial disease.

**Ten or fewer unrelated cases reported in the literature.*

*Four disorders listed in **Table 2**, complete DiGeorge anomaly, cartilage hair hypoplasia, IKAROS deficiency, and AR-HIES caused by DOCK8 deficiency, are also included in **Table 1** as they are characterized by striking T and B cell abnormalities. While not all DOCK8 deficient patients have elevated serum IgE, most have recurrent viral infections and malignancies as a result of combined immunodeficiency. AR-HIES due to TYK2 deficiency is also described in **Table 6**, because of its association with atypical mycobacterial disease resulting in MSMD. Because Riddle syndrome is caused by mutations in a gene involved in DNA double-strand break repair and is associated with hypogammaglobulinemia, we have added this rare syndrome to **Table 2**. Chronic mucocutaneous candidiasis (CMC) has been moved to **Table 6**. Autosomal dominant and autosomal recessive forms of Dyskeratosis congenita, caused by mutations of recently identified genes, have been included in this table. Finally, we added IKAROS deficiency, observed in a single case, a prematurely born infant, who died at the age of 87 days. He had absent B and NK cells and non-functional T cells, suggesting combined immunodeficiency.*

Table 3 | Predominantly antibody deficiencies.

Disease	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
1. Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells					
(a) BTK deficiency	All isotypes decreased in majority of patients; some patients have detectable immunoglobulins	Severe bacterial infections; normal numbers of pro-B cells	XL	Mutations in *BTK*, a cytoplasmic tyrosine kinase activated by crosslinking of the BCR	300300
(b) μ Heavy chain deficiency	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in μ heavy chain	147020
(c) λ5 deficiency*	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in λ5; part of the surrogate light chain in the pre-BCR	146770
(d) Igα deficiency*	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in Igα (*CD79a*); part of the pre-BCR and BCR	112205
(e) Igβ deficiency*	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in Igβ (*CD79b*); part of the pre-BCR and BCR	147245
(f) BLNK deficiency*	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells	AR	Mutations in *BLNK*; a scaffold protein that binds to BTK	604615
(g) Thymoma with immunodeficiency	One or more isotypes may be decreased	Bacterial and opportunistic infections; autoimmunity; decreased number of pro-B cells	None	Unknown	
(h) Myelodysplasia with hypogammaglobuline-mia	One or more isotypes may be decreased	Infections; decreased number of pro-B cells	Variable	May have monosomy 7, trisomy 8, or dyskeratosis congenita	
2. Severe reduction in at least 2 serum immunoglobulin isotypes with normal or low number of B cells					
(a) Common variable immunodeficiency disorders	Low IgG and IgA and/or IgM	Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias, and/or granulomatous disease	Variable	Unknown	
(b) ICOS deficiency*	Low IgG and IgA and/or IgM		AR	Mutations in *ICOS*	604558
(c) CD19 deficiency*	Low IgG and IgA and/or IgM	May have glomerulonephritis	AR	Mutations in *CD19*; transmembrane protein that amplifies signal through BCR	107265
(d) CD81 deficiency*	Low IgG, low or normal IgA, and IgM	May have glomerulonephritis	AR	Mutations in *CD81*; transmembrane protein that amplifies signal through BCR	186845
(e) CD20 deficiency*	Low IgG, normal or elevated IgM, and IgA		AR	Mutations in *CD20*	112210

(Continued)

Table 3 | Continued

Disease	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
(f) TACI deficiency	Low IgG and IgA and/or IgM	Variable clinical expression	AD or AR or complex	Mutations in *TNFRSF13B* (TACI)	604907
(g) BAFF receptor deficiency*	Low IgG and IgM	Variable clinical expression	AR	Mutations in *TNFRSF13C* (BAFF-R)	606269
3. Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells					
(a) CD40L deficiency	IgG and IgA decreased; IgM may be normal or increased; B cell numbers may be normal or increased	Opportunistic infections, neutropenia, autoimmune disease	XL	Mutations in *CD40LG* (also called *TNFSF5* or *CD154*)	300386
(b) CD40 deficiency*	Low IgG and IgA; normal or raised IgM	Opportunistic infections, neutropenia, autoimmune disease	AR	Mutations in *CD40* (also called *TNFRSF5*)	109535
(c) AID deficiency	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centers	AR	Mutations in *AICDA* gene	605257
(d) UNG deficiency	IgG and IgA decreased; IgM increased	Enlarged lymph nodes and germinal centers	AR	Mutations in *UNG*	191525
4. Isotype or light chain deficiencies with normal numbers of B cells					
(a) Ig heavy chain mutations and deletions	One or more IgG and/or IgA subclasses as well as IgE may be absent	May be asymptomatic	AR	Mutation or chromosomal deletion at 14q32	
(b) κ chain deficiency*	All immunoglobulins have lambda light chain	Asymptomatic	AR	Mutations in κ constant gene	147200
(c) Isolated IgG subclass deficiency	Reduction in one or more IgG subclass	Usually asymptomatic; a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections	Variable	Unknown	
(d) IgA with IgG subclass deficiency	Reduced IgA with decrease in one or more IgG subclass	Recurrent bacterial infections in majority	Variable	Unknown	
(e) Selective IgA deficiency	IgA decreased/absent	Usually asymptomatic; may have recurrent infections with poor antibody responses to carbohydrate antigens; may have allergies or autoimmune disease. A very few cases progress to CVID, others coexist with CVID in the family	Variable	Unknown	
5. Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells	Normal	Reduced ability to make antibodies to specific antigens	Variable	Unknown	

(Continued)

Table 3 | Continued

Disease	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
6. Transient hypogammaglobulinemia of infancy with normal numbers of B cells	IgG and IgA decreased	Normal ability to make antibodies to vaccine antigens, usually not associated with significant infections	Variable	Unknown	

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; BTK, Bruton tyrosine kinase; BLNK, B cell linker protein; AID, activation-induced cytidine deaminase; UNG, uracil-DNA glycosylase; ICOS, inducible costimulator; Igκ, immunoglobulin, or κ light chain type.
**Ten or fewer unrelated cases reported in the literature.*

*Two new autosomal recessive disorders that might previously have been called CVID have been added to **Table 3**. CD81 is normally co-expressed with CD19 on the surface of B cells. Like CD19 mutations, mutations in CD81 result in normal numbers of peripheral blood B cells, low serum IgG, and an increased incidence of glomerulonephritis. A single patient with a homozygous mutation in CD20 has been reported.*

*Common Variable Immunodeficiency Disorders (CVID) include several clinical and laboratory phenotypes that may be caused by distinct genetic and/or environmental factors. Some patients with CVID and no known genetic defect have markedly reduced numbers of B cells as well as hypogammaglobulinemia. Alterations in TNFRSF13B (TACI) and TNFRSF13C (BAFF-R) sequences may represent disease modifying mutations rather than disease causing mutations. CD40L and CD40 deficiency are included in **Table 1** as well as this table. A small minority of patients with XLP (**Table 4**), WHIM syndrome (**Table 6**), ICF (**Table 2**), VOD1 (**Table 2**), thymoma with immunodeficiency (Good syndrome) or myelodysplasia are first seen by an immunologist because of recurrent infections, hypogammaglobulinemia, and normal or reduced numbers of B cells. Patients with GATA2 mutations (**Table 5**) may have markedly reduced numbers of B cells, as well as decreased monocytes and NK cells and a predisposition to myelodysplasia but they do not have an antibody deficiency.*

Table 4 | Diseases of immune dysregulation.

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
1. Immunodeficiency with hypopigmentation							
(a) Chediak–Higashi syndrome	Normal	Normal	Normal	Partial albinism, recurrent infections, late-onset primary encephalopathy, increased lymphoma risk. Neutropenia, Giant lysosomes, low NK, and CTL activities, elevation of acute phase markers	AR	Mutations in *LYST*, impaired lysosomal trafficking	214500
(b) Griscelli syndrome, type2	Normal	Normal	Normal	Partial albinism, elevation of acute phase markers, encephalopathy in some patients. Low NK and CTL activities	AR	Mutations in *RAB27A* encoding a GTPase that promotes docking of secretory vesicles to the cell membrane	607624
(c) Hermansky–Pudlak syndrome, type 2*	Normal	Normal	Normal	Partial albinism, increased bleeding. Neutropenia, low NK, and CTL activity	AR	Mutations in the *AP3B1* gene, encoding for the β subunit of the AP-3 complex	608233
2. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes							
(a) Perforin deficiency, FHL2	Normal	Normal	Normal	Severe inflammation, persistent fever, cytopenias, splenomegaly. Hemophagocytosis, decreased to absent NK and CTL activities	AR	Mutations in *PRF1*; perforin, a major cytolytic protein	603553
(b) UNC13D (Munc13-4) deficiency, FHL3	Normal	Normal	Normal	Severe inflammation, persistent fever, splenomegaly, hemophagocytosis, decreased NK and CTL activities	AR	Mutations in *UNC13D** required to prime vesicles for fusion (*as named in OMIM). Note that also in OMIM the "official" name is UNC13D deficiency with the alternative title of MUNC13D deficiency	608898
(c) Syntaxin 11 deficiency, FHL4	Normal	Normal	Normal	Severe inflammation, persistent fever, splenomegaly. Hemophagocytosis, decreased to absent NK activity	AR	Mutations in *STX11*, required for fusion of secretory vesicles with the cell membrane and release of contents	603552
(d) STXBP2 (Munc 18-2) deficiency, FHL5	Normal	Normal	Normal or low	Severe inflammation, fever, splenomegaly, hemophagocytosis possible bowel disease. Decreased NK and CTL activities with partial restoration after IL-2 stimulation	AR	Mutations in *STXBP2*, required for fusion of secretory vesicles with the cell membrane and release of contents	613101

(Continued)

Table 4 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
3. Lymphoproliferative syndromes							
(a) SH2D1A deficiency, XLP1	Normal	Normal or reduced	Normal or low	Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, hemophagocytic syndrome, aplastic anemia, and lymphoma. Dysgammaglobulinemia or hypogammaglobulinemia, low to absent NKT cells	XL	Mutations in *SH2D1A* encoding an adaptor protein regulating intracellular signals	308240
(b) XIAP deficiency, XLP2	Normal	Normal or reduced	Normal or low	Clinical and immunologic abnormalities triggered by EBV infection, including splenomegaly, hepatitis, hemophagocytic syndrome colitis	XL	Mutations in *XIAP* encoding an inhibitor of apoptosis	300635
4. Syndromes with autoimmunity							
(a) Autoimmune lymphoproliferative syndrome (ALPS)							
(i) ALPS-FAS	Increased $CD4^-$ $CD8^-$ double negative (DN) T cells	Normal, but increased number of $CD5^+$ B cells	Normal or increased	Splenomegaly, adenopathies, autoimmune cytopenias, increased lymphoma risk. Defective lymphocyte apoptosis	AD (AR cases are rare and severe)	Mutations in *TNFRSF6*, cell surface apoptosis receptor; in addition to germline mutations, somatic mutations cause a similar phenotype (ALPS-sFAS)	601859
(ii) ALPS-FASLG	Increased DN T cells	Normal	Normal	Splenomegaly, adenopathies, autoimmune cytopenias, SLE defective lymphocyte apoptosis	AD AR	Mutations in *TNFSF6*, ligand for CD95 apoptosis receptor	134638
(iii) ALPS-CASP10*	Increased DN T cells	Normal	Normal	Adenopathies, splenomegaly, autoimmunity. Defective lymphocyte apoptosis	AD	Mutations in *CASP10*, intracellular apoptosis pathway	603909
(iv) Caspase 8 defect*	Slightly increased DN T cells	Normal	Normal or decreased	Adenopathies, splenomegaly, recurrent bacterial, and viral infections. Defective lymphocyte apoptosis and activation, hypogammaglobulinemia	AD	Mutations in *CASP8*, intracellular apoptosis and activation pathways	607271
(v) Activating N-RAS defect, activating K-RAS defect*	Increased or normal DN T cells	Elevation of CD5 B cells	Normal	Adenopathies, splenomegaly, leukemia, lymphoma. Defective lymphocyte apoptosis following IL-2 withdrawal	Sporadic	Somatic mutations in *NRAS* encoding a GTP binding protein with diverse signaling functions; activating mutations impair mitochondrial apoptosis	164790

(Continued)

Table 4 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
(vi) FADD deficiency*	Increased DN T cells	Normal	Normal	Functional hyposplenism, recurrent bacterial, and viral infections, recurrent episodes of encephalopathy and liver dysfunction. Defective lymphocyte apoptosis	AR	Mutations in *FADD* encoding an adaptor molecule interacting with FAS, and promoting apoptosis, inflammation and innate immunity	613759
(b) APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Normal	Normal	Normal	Autoimmunity, particularly of parathyroid, adrenal, and other endocrine organs, chronic candidiasis, dental enamel hypoplasia, and other abnormalities	AR	Mutations in *AIRE*, encoding a transcription regulator needed to establish thymic self-tolerance	240300
(c) IPEX, immune dysregulation, polyendocrinopathy, enteropathy (X-linked)	Lack of (and/or impaired function of) $CD4^+$ $CD25^+$ $FOXP3^+$ regulatory T cells	Normal	Elevated IgA, IgE	Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema	XL	Mutations in *FOXP3*, encoding a T cell transcription factor	304790
(d) CD25 deficiency	Normal to modestly decreased	Normal	Normal	Lymphoproliferation, autoimmunity. Impaired T cell proliferation	AR	Mutations in IL-2Rα chain	606367
(e) ITCH deficiency*	Not assessed (Th2 skewing in *Itch*-deficient mice)	Not assessed (B cells are dysfunctional in *Itch*-deficient mice)	Not assessed (elevated in *Itch*-deficient mice)	Multi-organ autoimmunity, chronic lung disease, failure to thrive, developmental delay, macrocephaly	AR	Mutations in *ITCH*, an E3 ubiquitin ligase	613385

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; DN, double negative; SL, systemic lupus erythematosus.
**Ten or fewer unrelated cases reported in the literature.*

*STXBP2/Munc18-2 deficiency has been added as the cause of "FHL5," a new form of FHL. Of note, "FHL1" has not yet received a genetic/molecular identification. FADD deficiency is classified among the causes of ALPS. It should be stressed however that FADD deficiency is a more complex syndrome that encompasses hyposplenism, hence bacterial infections, as well as a brain and liver primary dysfunction. EBV-driven lymphoproliferation is also observed in ITK deficiency and in MAGT1 deficiency (**Table 1**).*

Table 5 | Congenital defects of phagocyte number, function, or both.

Disease	Affected cells	Affected function	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
1. Defects of neutrophil differentiation						
(a) Severe congenital neutropenia1 (ELANE deficiency)	N	Myeloid differentiation	Subgroup with myelodysplasia	AD	*ELANE:* misfolded protein response	202700
(b) SCN2* (GFI 1 deficiency)	N	Myeloid differentiation	B/T lymphopenia	AD	*GFI*1: loss of repression of ELANE	613107
(c) SCN3 (Kostmann disease)	N	Myeloid differentiation	Cognitive and neurological defects in some patients	AR	*HAX*1:control of apoptosis	610738
(d) SCN4 (G6PC3 deficiency)	N + F	Myeloid differentiation, chemotaxis, O_2^- production	Structural heart defects, urogenital abnormalities, and venous angiectasis of trunks and limbs	AR	*G6PC*3: abolished enzymatic activity of glucose-6-phosphatase, aberrant glycosylation, and enhanced apoptosis of neutrophils and fibroblasts	612541
(e) Glycogen storage disease type 1b	N + M	Myeloid differentiation, chemotaxis, O_2^- production	Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly	AR	*G6PT*1: glucose-6-phosphate transporter 1	232220
(f) Cyclic neutropenia	N	?	Oscillations in the number of other leukocytes and platelets	AD	*ELANE*: misfolded protein response	162800
(g) X-linked neutropenia/* myelodysplasia	N + M	Mitosis	Monocytopenia	XL	*WAS:* regulator of actin cytoskeleton (loss of autoinhibition)	300299
(h) P14 deficiency*	N + L Mel	Endosome biogenesis	Neutropenia Hypogammaglobulinemia ↓CD8 cytotoxicity partial albinism growth failure	AR	*ROBLD*3: endosomal adaptor protein 14	610389
(i) Barth syndrome	N	Myeloid differentiation	Cardiomyopathy, growth retardation	XL	Tafazzin (*TAZ*) gene: abnormal lipid structure of mitochondrial membrane	302060
(j) Cohen syndrome	N	Myeloid differentiation	Retinopathy, developmental delay, facial dysmorphisms	AR	*COH*1 gene: Pathogenesis unknown	216550
(k) Poikiloderma with neutropenia	N	Myeloid differentiation, O_2^- production	Poikiloderma, MDS	AR	*C*16*orf*57 gene: Pg unknown	604173
2. Defects of motility						
(a) Leukocyte adhesion deficiency type 1 (LAD1)	N + M + L + NK	Adherence, chemotaxis, endocytosis, T/NK cytotoxicity	Delayed cord separation, skin ulcers periodontitis leukocytosis	AR	*INTGB*2: adhesion protein (CD18)	116920

(Continued)

Table 5 | Continued

Disease	Affected cells	Affected function	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
(b) Leukocyte adhesion deficiency type 2 (LAD2)*	N + M	Rolling, chemotaxis	Mild LAD type 1 features plus hh-blood group plus mental and growth retardation	AR	*FUCT*1: GDP-Fucose transporter	266265
(c) Leukocyte adhesion deficiency type 3 (LAD3)	N + M + L + NK	Adherence, chemotaxis	LAD type 1 plus bleeding tendency	AR	*KINDLIN*3: Rap1-activation of β1-3 integrins	612840
(d) Rac 2 deficiency*	N	Adherence, chemotaxis O_2^- production	Poor wound healing, leukocytosis	AD	*RAC*2: Regulation of actin cytoskeleton	602049
(e) β-actin deficiency*	N + M	Motility	Mental retardation, short stature	AD	*ACTB*: cytoplasmic actin	102630
(f) Localized juvenile periodontitis	N	Formyl peptide induced chemotaxis	Periodontitis only	AR	*FPR*1: chemokine receptor	136537
(g) Papillon–Lefèvre syndrome	N + M	Chemotaxis	Periodontitis, palmoplantar hyperkeratosis in some patients	AR	*CTSC*: cathepsin C: abnormal activation of serine proteases	245000
(h) Specific granule deficiency*	N	Chemotaxis	Neutrophils with bilobed nuclei	AR	*C/EBPE*: myeloid transcription factor	245480
(i) Shwachman–Diamond syndrome	N	Chemotaxis	Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia	AR	*SBDS:* defective ribosome synthesis	260400
3. Defects of respiratory burst						
(a) X-linked chronic granulomatous disease (CGD)	N + M	Killing (faulty O_2^- production)	McLeod phenotype in patients with deletions extending into the contiguous Kell locus	XL	*CYBB*: electron transport protein (gp91phox)	306400
(b-e) Autosomal CGD's	N + M	Killing (faulty O_2^- production)		AR	*CYBA*: electron transport protein (p22phox) *NCF*1: adapter protein (p47phox) *NCF*2: activating protein (p67phox) *NCF*4: activating protein (p40 phox)	233690 233700 233710 601488
4. MSMD						
(a) IL12 and IL23 receptor β1 chain deficiency	L + NK	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IL12RB*1: IL12 and IL23 receptor β1 chain	601604
(b) IL12p40 deficiency	M	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IL12B*: subunit of IL12/IL23	161561
(c) IFN-γ receptor 1 deficiency	M + L	IFN-γ binding and signaling	Susceptibility to *Mycobacteria* and *Salmonella*	AR, AD	*IFNGR*1: IFN-γR ligand binding chain	107470

(Continued)

Table 5 | Continued

Disease	Affected cells	Affected function	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
(d) IFN-γ receptor 2 deficiency	M + L	IFN-γsignaling	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IFNGR*2: IFN-γR accessory chain	147569
(e) STAT1 deficiency (AD form)*	M + L	IFN-γsignaling	Susceptibility to *Mycobacteria, Salmonella*	AD	*STAT*1	600555
(f) Macrophage gp91 phox deficiency*	Mϕ only	Killing (faulty O_{2^-} production)	Isolated susceptibility to mycobacteria	XL	*CYBB: electron transport protein* (*gp* 91 *phox*)	306400
(g) IRF8 deficiency (AD form)*	$CD1c^+$ MDC	Differentiation of $CD1c^+$ MDC subgroup	Susceptibility to *Mycobacteria*	AD	*IRF*8*:* IL12 production by $CD1c^+$ MDC	601565
5. Other defects						
(a) IRF 8-deficiency (AR form)*	Monocytes periph-eral DC	Cytopenias	Susceptibility to *Mycobacteria*, Candida, myeloproliferation	AR	*IRF*8: IL12 production	
(b) GATA2 deficiency (Mono MAC Syndrome)	Monocytes periph-eral DC + NK + B	Multilineage cytopenias	Susceptibility to *Mycobacteria*, Papilloma Viruses, Histoplasmosis, Alveolar proteinosis, MDS/AML/CMML	AD	*GATA*2: loss of stem cells	137295
(c) Pulmonary alveolar proteinosis*	Alveolar macro-phages	GM-CSF signaling	Alveolar proteinosis	Biallelic mutations in pseudoauto-somal gene	*CSF*2*RA*	306250

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; ACTB, actin beta; B, B-lymphocytes; CEBPE, CCAAT/enhancer-binding protein epsilon; CMML, chronic myelomonocytic leukaemia; CTSC, cathepsin C; CYBA, cytochrome b alpha subunit; CYBB, cytochrome b beta subunit; DC, dendritic cells; ELANE, elastase neutrophil-expressed; GATA2, GATA binding protein 2; IFN, interferon; IFNGR1, interferon-gamma receptor subunit 1; IFNGR2, interferon-gamma receptor subunit 2; IL12B, interleukin-12 beta subunit; IL12RB1, interleukin-12 receptor beta 1; IFR8, interferon regulatory factor 8; F, fibroblasts; FPR1, formyl peptide receptor 1; FUCT1, fucose transporter 1; GFI1, growth factor independent 1; HAX1, HLCS1-associated protein X1; ITGB2, integrin beta-2; L, lymphocytes; M, monocytes–macrophages; MDC, myeloid dendritic cells; MDS, myelodysplasia; Mel, melanocytes; Mϕ, macrophages; MSMD, Mendelian susceptibility to mycobacterial disease; N, neutrophils; NCF1, neutrophil cytosolic factor 1; NCF2, neutrophil cytosolic factor 2; NCF4, neutrophil cytosolic factor 4; NK, natural killer cells; ROBLD3, roadblock domain containing 3; SBDS, Shwachman–Bodian–Diamond syndrome; STAT, signal transducer and activator of transcription.
**Ten or fewer unrelated cases reported in the literature.*

***Table 5** includes seven newly described genetic defects of phagocyte number and/or function including Barth syndrome, Cohen syndrome and Poikiloderma with neutropenia. In these three clinically well-known diseases the genetic defects have been elucidated, although their molecular pathogenesis remains ill-defined. A new cause of autosomal recessive chronic granulomatous disease, namely a deficiency of the cytosolic activating protein p40 phox, has now been found in two CGD patients and is included under defects of respiratory burst. Under the heading of Mendelian susceptibility of mycobacterial disease (MSMD) two new entities were added: a) a subgroup of X-linked gp91 phox deficiency with isolated susceptibility to mycobacteria and a defect of the respiratory burst in macrophages only; b) an autosomal dominant form of IRF8 deficiency, resulting from a lack of $CD1c^+$ myeloid dendritic cells that would normally secrete IL12. The clinical phenotype of MSMD may vary, depending on the nature of the genetic defect. Finally GATA2 deficiency was recently identified as the cause of the Mono MAC syndrome, with multilineage cytopenias (of monocytes, peripheral dendritic cells, NK- and B-lymphocytes) resulting in opportunistic infections (including mycobacteria), alveolar proteinosis and malignancy.*

Table 6 | Defects in innate immunity.

Disease	Affected cell	Functional defect	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
1. Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)						
(a) EDA-ID, X-linked (NEMO deficiency)	Lymphocytes + monocytes	NFκB signaling pathway	Anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of Ab response to polysaccharides) + various infections (mycobacteria and pyogenes)	XL	Mutations of NEMO (*IKBKG*), a modulator of NF-κB activation	300291, 300584, 300301
(b) EDA-ID, autosomal dominant*	Lymphocytes + monocytes	NFκB signaling pathway	Anhidrotic ectodermal dysplasia + T cell defect + various infections	AD	Gain-of-function mutation of *IKBA*, resulting in impaired activation of NF-κB	612132
2. IRAK4 deficiency	Lymphocytes + monocytes	TIR-IRAK signaling pathway	Bacterial infections (pyogenes)	AR	Mutation of *IRAK*4, a component of TLR- and IL-1R-signaling pathway	607676
3. MyD88 deficiency	Lymphocytes + monocytes	TIR-MyD88 signaling pathway	Bacterial infections (pyogenes)	AR	Mutation of *MYD*88, a component of the TLR and IL-1R-signaling pathway	612260
4. WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome	Granulocytes + lymphocytes	Increased response of the CXCR4 chemokine receptor to its ligand CXCL12 (SDF-1)	Hypogammaglobulinemia, reduced B cell number, severe reduction of neutrophil count, warts/HPV infection	AD	Gain-of-function mutations of *CXCR*4, the receptor for CXCL12	193670
5. Epidermodysplasia verruciformis	Keratinocytes and leukocytes		Human Papilloma virus (group B1) infections and cancer of the skin	AR	Mutations of *EVER*1, *EVER*2	226400
6. Herpes simplex encephalitis (HSE)*						
(a) TLR3 deficiency*	Central nervous system (CNS) resident cells and fibroblasts	TLR3-dependent IFN-α, -β, and -λ induction	Herpes simplex virus 1 encephalitis	AD	Mutations of *TLR*3	613002
(b) UNC93B1 deficiency	CNS resident cells and fibroblasts	UNC-93B-dependent IFN-α, -β, and -λ induction	Herpes simplex virus 1 encephalitis	AR	Mutations of *UNC*93*B*1	610551
(c) TRAF3 deficiency	CNS resident cells and fibroblasts	TRAF3-dependent IFN-α, -β, and -λ induction	Herpes simplex virus 1 encephalitis	AD	Mutation of *TRAF*3	
7. Predisposition to fungal diseases*	Mononuclear phagocytes	CARD9 signaling pathway	Invasive candidiasis and peripheral dermatophytosis	AR	Mutations of *CARD*9	212050
8. Chronic mucocutaneous candidiasis (CMC)						
(a) IL-17RA deficiency*	Epithelial cells, fibroblasts, mononuclear phagocytes	IL-17RA signaling pathway	CMC	AR	Mutation in *IL-17RA*	605461
(b) IL-17F deficiency*	T cells	IL-17F-containing dimers	CMC	AD	Mutation in *IL-17F*	606496

(Continued)

Table 6 | Continued

Disease	Affected cell	Functional defect	Associated features	Inheritance	Genetic defect/presumed pathogenesis	OMIM number
(c) STAT1 gain-of-function	T cells	Gain-of-function STAT1 mutations that impair the development of IL-17-producing T cells	CMC	AD	Mutations in *STAT1*	614162
9. Trypanosomiasis*		APOL-I	Trypanosomiasis	AD	Mutation in *APOL-I*	603743

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; NF-κB, nuclear factor κ B; TIR, toll and interleukin 1 receptor; IFN, interferon; HP, human papilloma virus; TLR, toll-like receptor; IL: interleukin.
**Ten or fewer unrelated cases reported in the literature.*

*Four new disorders have been added to **Table 6**. AD TRAF3 deficiency is a new genetic etiology of HSE that has been diagnosed in a single patient. A new entry in the Table is CMC, for which three genetic etiologies have been discovered. AR IL-17RA deficiency and AD IL-17F deficiency have been found in one kindred each. Gain-of-function mutations in STAT1 have been found in over 50 patients with AD CMC. The mechanism of CMC in these patients involves impaired development of IL-17-producing T cells, due to the hyperactivity of STAT1-dependent signals.*

XR-EDA-ID is highly heterogeneous clinically, both in terms of developmental features (some patients display osteopetrosis and lymphedema, in addition to EDA, while others do not display any developmental features) and infectious diseases (some display multiple infections, viral, fungal, and bacterial, while others display a single type of infection). The various OMIM entries correspond to these distinct clinical diseases.

Table 7 | Autoinflammatory disorders.

Disease	Affected cells	Functional defects	Associated Features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
1. Defects effecting the inflammasome						
(a) Familial Mediterranean fever	Mature granulocytes, cytokine-activated monocytes	Decreased production of pyrin permits ASC-induced IL-1 processing and inflammation following subclinical serosal injury; macrophage apoptosis decreased	Recurrent fever, serositis and inflammation responsive to colchicine. Predisposes to vasculitis and inflammatory bowel disease	AR	Mutations of *MEFV*	249100
(b) Hyper IgD syndrome		Mevalonate kinase deficiency affecting cholesterol synthesis; pathogenesis of disease unclear	Periodic fever and leukocytosis with high IgD levels	AR	Mutations of *MVK*	260920
(c) Muckle–Wells syndrome	PMNs monocytes	Defect in cryopyrin, involved in leukocyte apoptosis and NFkB signaling and IL-1 processing	Urticaria, SNHL, amyloidosis	AD	Mutations of *CIAS*1(also called *PYPAF*1 *or NALP*3)	191900
(d) Familial cold autoinflammatory syndrome	PMNs, monocytes	same as above	Non-pruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure	AD	Mutations of *CIAS*1 Mutations of *NLRP*12	120100
(e) Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA)	PMNs, chondrocytes	same as above	Neonatal onset rash, chronic meningitis, and arthropathy with fever and inflammation	AD	Mutations of *CIAS*1	607115
2. Non-inflammasome-related conditions						
(a) TNF receptor-associated periodic syndrome (TRAPS)	PMNs, monocytes	Mutations of 55-kD TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF	Recurrent fever, serositis, rash, and ocular or joint inflammation	AD	Mutations of *TNFRSF*1*A*	142680
(b) Early onset inflammatory bowel disease	Monocyte/ macrophage, activated T cells	Mutation in IL-10 or IL-10 receptor leads to increase of TNFγ and other proinflammatory cytokines	Early onset enterocolitis enteric fistulas, perianal abscesses, chronic folliculitis	AR	Mutations in *IL10, IL*10*RA*, or *IL*10*RB*	146933
(c) Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome	Hematopoietic tissues, upregulated in activated T cells	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	Destructive arthritis, inflammatory skin rash, myositis	AD	Mutations of *PSTPIP*1 (also called C2BP1)	604416

(Continued)

Table 7 | Continued

Disease	Affected cells	Functional defects	Associated Features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
(d) Blau syndrome	Monocytes	Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and NF-κB signaling	Uveitis, granulomatous synovitis, camptodactyly, rash, and cranial neuropathies, 30% develop Crohn's disease	AD	Mutations of *NOD2* (also called CARD15)	186580
(e) Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)*	Neutrophils, bone marrow cells	Undefined	Chronic recurrent multifocal osteomyelitis, transfusion-dependent anemia, cutaneous inflammatory disorders	AR	Mutations of *LPIN2*	609628
(f) DIRA (Deficiency of the interleukin 1 receptor antagonist)*	PMNs, monocytes	Mutations in the IL1 receptor antagonist allows unopposed action of interleukin 1	Neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis	AR	Mutations of *IL1RN*	612852

AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; PMN, polymorphonuclear cells; ASC, apoptosis-associated speck-like protein with a caspase recruitment domain; CARD, caspase recruitment domain; CD2BP1, CD2 binding protein 1; PSTPIP1, proline/serine/threonine phosphatase-interacting protein 1; SNHL, sensorineural hearing loss; CIAS1, cold-induced autoinflammatory syndrome 1.

**Ten or fewer unrelated cases reported in the literature.*

Autoinflammatory diseases are clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition. While the genetic defect of one of the most common autoinflammatory conditions, PFAPA, is not known, recent studies suggest that it is associated with activation of IL-1 pathway and response to IL-1 beta antagonists.

Muckle–Wells syndrome, familial cold autoinflammatory syndrome, and neonatal onset multisystem inflammatory disease (NOMID) which is also called chronic infantile neurologic cutaneous and articular syndrome (CINCA) are caused by similar mutations in CIAS1 mutations. The disease phenotype in any individual appears to depend on modifying effects of other genes and environmental factors.

Table 8 | Complement deficiencies.

Disease	Functional defect	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
C1q deficiency	Absent CH50 hemolytic activity, defective MAC, faulty dissolution of immune complexes, faulty clearance of apoptotic cells	SLE-like syndrome, rheumatoid disease, infections	AR	Mutations in *C1QA*, *C1QB*, *C1QC*, and loss of early complement activation	120550; 601269; 120575
C1r deficiency	Absent CH50 hemolytic activity, defective MAC, faulty dissolution of immune complexes	SLE-like syndrome, rheumatoid disease, multiple autoimmune diseases, infections	AR	Mutations in C1r and loss of early complement activation	216950
C1s deficiency	Absent CH50 hemolytic activity	SLE-like syndrome; multiple autoimmune diseases	AR	Mutations in C1s and loss of early complement activation	120580
C4 deficiency	Absent CH50 hemolytic activity, defective MAC, faulty dissolution of immune complexes, defective humoral immune response to carbohydrate antigens in some patients	SLE-like syndrome, rheumatoid disease, infections *C4A*; homozygous; SLE, type I diabetes *C4B:* homozygous: bacterial meningitis	AR	Mutations in *C4A* and *C4B* and loss of early complement activation	120810; 120820
C2 deficiency	Absent CH50 hemolytic activity, defective MAC, faulty dissolution of immune complexes	SLE-like syndrome, vasculitis, atherosclerosis, polymyositis, pyogenic infections; glomerulonephritis	AR	Mutations in *C2* and loss of early complement activation	217000
C3 deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity, defective humoral immune response	Life threatening pyogenic infections; SLE-like disease; glomerulonephritis; atypical hemolytic–uremic syndrome; selected SNPs with age related macular degeneration	AR	Mutations in *C3* and loss of complement activation by classical and alternative pathways	120700
C5 deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity	Neisserial infections, SLE	AR	Mutations in *C5*α? or *C5*β? and loss of complement activation	120900
C6 deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity	Neisserial infections, SLE	AR	Mutations in *C6* and loss of complement activation	217050
C7 deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity	Neisserial infections, SLE, vasculitis	AR	Mutations in *C7* and loss of terminal complement activation	217070
C8a deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity	Neisserial infections, SLE	AR	Mutations in *C8*α and loss of terminal complement activation	120950
C8b deficiency	Absent CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity	Neisserial infections, SLE	AR	Mutations in *C8*β and loss of terminal complement activation	120960
C9 deficiency	Reduced CH50 and AP50 hemolytic activity, defective MAC, defective bactericidal activity	Neisserial infections, weaker association than in C5, C6, C7, or C8 deficiency	AR	Mutations in *C9* and loss of terminal complement activation	613825

(Continued)

Table 8 | Continued

Disease	Functional defect	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
C1 inhibitor deficiency	Spontaneous activation of the complement pathway with consumption of C4/C2, spontaneous activation of the contact system with generation of bradykinin from high molecular weight kininogen	Hereditary angioedema	AD	Mutations in *C*1 inhibitor and loss of regulation of proteolytic activities of complement C1	138470
Factor D deficiency	Absent AP50 hemolytic activity	Severe neisserial infection	AR	Mutations in factor D (*CFD*), impairing alternative complement activation	134350
Properdin deficiency	Absent AP50 hemolytic activity	Severe neisserial infection	XL	Mutations in properdin (*PFC*), impairing alternative complement activation	312060
Factor I deficiency	Spontaneous activation of the alternative complement pathway with consumption of C3	Recurrent pyogenic infections, glomerulonephritis, SLE; hemolytic–uremic syndrome; selected SNPS: severe pre-eclampsia	AR	Mutations in factor I(*CFI*), leading to accelerated catabolism of C3	610984
Factor H deficiency	Spontaneous activation of the alternative complement pathway with consumption of C3	Hemolytic–uremic syndrome, membranoproliferative glomerulonephritis; neisserial infections; selected SNPS: severe pre-eclampsia	AR	Mutations in factor H(*CFH*), leading to continuous activation of the alternative complement pathway and C3 deposition in tissues	609814
MASP1 deficiency	Potential loss of embryonic cell migration signals	A developmental syndrome of facial dysmorphism, cleft lip, and/or palate, craniosynostosis, learning disability and genital, limb and vesicorenal anomalies	AR	Mutations in *MASP*1 leading to impaired complement pathway through the mannan-binding lectin serine proteases	600521
3MC syndrome COLEC11 deficiency	Potential loss of embryonic cell migration signals	A developmental syndrome of facial dysmorphism, cleft lip and/or palate, craniosynostosis, learning disability and genital, limb and vesicorenal anomalies	AR	Gene product CL-K1, a C-type lectin that may serve as a chemoattractant	612502
MASP2 deficiency*	Absent hemolytic activity by the lectin pathway	Pyogenic infections; inflammatory lung disease	AR	Mutations in *MASP*2 leading to impaired complement pathway through the mannan-binding lectin serine proteases	605102
Complement receptor 3 (CR3) deficiency	See LAD1 in **Table 5**		AR	Mutations in *INTGB*2	116920
Membrane cofactor protein (CD46) deficiency	Inhibitor of complement alternate pathway, decreased C3b binding	Glomerulonephritis, atypical hemolytic–uremic syndrome; selected SNPS: severe pre-eclampsia	AD	Mutations in *MCP* leading to loss of the cofactor activity needed for the factor I-dependent cleavage of C3B and C4B	120920
Membrane attack complex inhibitor (CD59) deficiency	Erythrocytes highly susceptible to complement-mediated lysis	Hemolytic anemia, thrombosis	AR	Mutations in *CD*59 leading to loss of this membrane inhibitor of the membrane attack complexes	107271

(Continued)

Table 8 | Continued

Disease	Functional defect	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
Paroxysmal nocturnal hemoglobinuria	Complement-mediated hemolysis	Recurrent hemolysis; hemoglobinuria, abdominal pain, smooth muscle dystonias, fatigue, and thrombosis	Acquired X-linked mutation	Disease results from the expansion of hematopoietic stem cells bearing mutations in *PIGA* and subsequent loss of biosynthesis of glycosylphosphatidylinositol (GPI) a moiety that attaches proteins to the cell surface.	300818
Immunodeficiency associated with Ficolin 3 deficiency*	Absence of complement activation by the Ficolin 3 pathway.	Recurrent severe pyogenic infections mainly in the lungs; necrotizing enterocolitis in infancy; selective antibody defect to pneumococcal polysaccharides	AR	Mutations in *FCN*3, leading to impaired complement deposition	604973

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; MAC, membrane attack complex; SLE, systemic lupus erythematosus; MBP, Mannose binding Protein; MASP2, MBP associated serine protease 2.

**Ten or fewer unrelated cases reported in the literature.*

*New entities added to **Table 8** demonstrate the important role of complement regulators in a group of well-described inflammatory disorders. In particular, we have added mutations in membrane bound as well as surface attached soluble complement regulatory proteins recognized in hemolytic–uremic syndrome, age related macular degeneration and pre-eclampsia. The connecting theme of these otherwise unrelated clinical events is excessive activation or insufficient regulation of C3; these events lead to recruitment of leukocytes and permit secretion of inflammatory and anti-angiogenic mediators that disrupt the vascular bed of the target organ. Alterations in the genes for factor B (CFB), factor I (CFI), factor H (CFH), and CD46 act as susceptibility genes rather than disease causing mutations. Population studies reveal no detectable increase in infections in MBP (also known at mannose binding lectin – MBL) deficient adults. The 3MC syndrome, a developmental syndrome, has been variously called Carnevale, Mingarelli, Malpuech, and Michels syndrome.*

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